SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina

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La giusta durata
della terapia antibiotica per i quadri infettivi più` frequenti

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Disclosure

Scientific boards, travel expenses, research grants

- MSD
- Angelini
- Pfizer
- Shionogi
- Menarini
- Biomeriuex

Types of AMS interventions: stopping therapy

Trade one broad-spectrum regimen for another

Narrow the spectrum based on culture and susceptibility results

Patients doing well; change to po and/or discharge

Patient cured; discontinue therapy

Resistance effect	Cost effectiveness
Little effect	Little effect
Large effect	Large effect
Large effect	Enormous effect
Large effect	Large effect

J Antimicrob Chemother 2018; **73**: 1084–1090
doi:10.1093/jac/dkx528 Advance Access publication 16 January 2018

Journal of Antimicrobial Chemotherapy

Are infection specialists recommending short antibiotic treatment durations? An ESCMID international cross-sectional survey

Gabriel Macheda[1], Oliver J. Dyar[2], Amandine Luc[3], Bojana Beovic[4,5], Guillaume Béraud[6–8], Bernard Castan[9], Rémy Gauzit[10], Philippe Lesprit[11], Pierre Tattevin[12], Nathalie Thilly[3,13] and Céline Pulcini[1,13]* on behalf of ESGAP and SPILF

Conclusions:

The majority of infection specialists currently *do not advise the shortest possible duration* of antibiotic therapy to prescribers.

Promoting short durations among these experts is urgently needed.

Table 5. Prevalence of short durations of antibiotic therapy and shortened durations by country

	N	Percentage short treatment[a]	Percentage shortened duration[b]
Argentina	29	10.7	42.3
Austria	37	20.8	84.2
France	165	46.0	50.4
Germany	79	63.6	60.7
Greece	13	0	54.6
Ireland	16	0	46.7
Israel	26	17.4	38.1
Italy	23	6.7	38.5
Netherlands	13	38.5	33.3
Slovenia	39	12.5	51.9
South Africa	16	73.3	35.7
Spain	82	44.4	46.0
Sweden	22	10.0	33.3
Turkey	18	13.3	55.6
UK	136	40.2	32.1
Uruguay	17	18.8	53.3

[a]Percentage of respondents advising short duration of therapy in more than 50% of the vignettes.

Antibiotics :
The Double-Edged Sword of Modern Medicine

Fundamental problems of AMS

START ANTIBIOTICS

- ✓ The easiest thing to do in medicine is to

STOP ANTIBIOTICS

- ✓ The **hardest thing to do!**
- ✓ The most common question is

"How many more days of antibiotics?"

- ✓ Not enough doctors ask

"Does this patient need antibiotics?"

Fundamental barriers to AMS compliance

START ANTIBIOTICS

- ✓ Limitation in Decision-making autonomy

STOP ANTIBIOTICS

- ✓ **Limitations of international&local evidence–based policies**
- ✓ Lack of Diagnostic tools & biomarkers
- ✓ Culture behavior/ team work/ hierarchy

I would definitely push my case
My patient is more critical

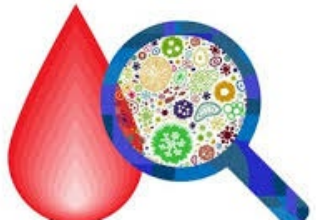
E. Charani et al. CID 2013:57 (15 July) & Differences in Antibiotic Decision-making; CID 2019:69 (1 July)

Recommended durations: *Shorter is better*

Evidence from RCTs and observational studies

BSI: antibiotic treatment duration

Type of infection	Duration	Evidence from RCTs, systematic meta-analysis and observational studies
Gram-negative bacteremia	**7** vs 14 days	Molina J,. Clin Microbiol Infect. 2022 Apr;28(4):550-557 Von Dach E, JAMA. 2020 Jun 2;323(21):2160-2169. Yahav et al., Clin Infect Dis 2019; 69:1091 (except for *IDs and cBSI)*
Streptococcal bacteraemia	**7-10** vs 11-18 days	***No data from RCT*** Nicolas Fourré, Journal of Infection, **(2024)**
VRE BSI	**7 vs** 14 days	***No data from RCT*** Christina Bahrs et al. Clinical Microbiology and Infection 29 **(2023)** 200e207 DESTINi
P. aeruginosa BSI	**10** days	***No data from RCT*** Fabre, Clin Infect Dis. 2019 Nov 13;69(11):2011-2014. Babich T, Naucler P, Infect Dis Ther 2022;11:1505e19. Bae M, J Antimicrob Chemother 2021;77:223e8.
Catheter-Related Septic Thrombosis	**≤21 days** vs >21 days (NO fungal and *S. aureus)*	***No data from RCT*** Stoldick M, Open Forum Infect Dis. **2023** Oct 25;10(11):ofad530.

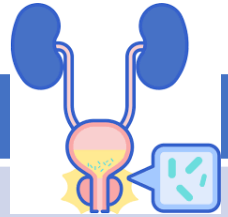


RTIs: antibiotic treatment duration

Type of infection	Duration	Evidence from RCTs and systematic meta-analysis
Acute bacterial sinusitis	3- 5 vs 7 days	Henry DC, Antimicrob Agents Chemother. 2003;47(9):2770-2774. Rosenfeld et al., Otolaryngol Head Neck Surg 2015; 152:S1 + other 4 RCTs
Acute Exacerbation Chronic Bronchitis/COPD	2- vs 7 days	El Moussaoui R, Thorax 2008; 63(5):415-22. Messous S, Ther Advanc Resp Dis. 2022. 16:175.
CAP	3-5 days vs 7-14 days	Mandell LA, Clin Inf Dis 2007; Tellier G, J Antimicrob Chemother 2004 Tansarli et al. Antimicrob Agents Chemother 2018; 62 Uranga A, JAMA Intern Med. 2016 Sep 1;176(9):1257-65 Bielicki J, JAMA. 2021;326(17):1713-1724. **Dinh A, Lancet. 2021 Mar 27;397(10280):1195-1203.** Williams DJ. JAMA Pediatrics. 2022. 176(3):253-261. McCallum G, Ped Infect Dis J. 2022. 41(7):549-555. Israelsen SB, Clin Microbiol Infect. **2023** Jan;29(1):54-60
HCAP, VAP	8 days vs 10-15	Kalil AC et al., Clin Infect Dis 2016; 63:e61 Pugh et al., Cochrane Database Syst Rev 2015; :CD007577 (except for *bacteremia, slow response to therapy, immunocompromise, and pyogenic complications)* Torres et al., Eur Respir J 2017; 50 Mo Y,. Lancet Resp Med. **2024** (**REGARD-VAP**)
Empyemas	2-3 weeks vs 5-6 weeks if source control is adequate with chest tubes.	Porcel JM, Pleura Peritoneum. 2020 Feb 26;5(1):20190027. Hassan M, Gad-Allah M, El-Shaarawy B, et al. The Short versus Long Antibiotic Course for Pleural Infection Management (SLIM) randomised controlled open-label trial. ERJ Open Res. **2023** Apr 11;9(2):00635-2022.

Meschiari's personal elaboration

UTI & IAIs : antibiotic treatment duration

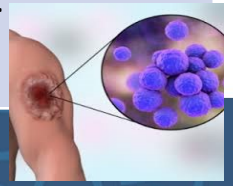


Type of infection	Duration	Evidence from RCTs
Uncomplicated cystitis	3- vs 5 days	Gupta K, Clin Infect Dis 2011 Huttner et al. J Antimicrob Chemother 2015; 70:2456
Pyelonephritis	7 –vs 14 days	Gupta K, Clin Infect Dis 2011 9 Van Nieuwkoop C et al., BMC Med 2017; 15:70 Erba, Internal and Emergency Medicine (2021) 16:313–323 + other 11 RCTs
Catheter-associated UTI	7- vs 10 days	Gupta K, Clin Infect Dis 2011 Hooton et al. Clin Infect Dis 2010;50:625–663
Men UTIs	7 vs 10 days	Drekonja DM,JAMA. 2021;326(4):324–331. *(ciprofloxacin or trimethoprim/sulfamethoxazole)*
Intra-abdominal infections	5-8 days vs 14 days	Solomkin JS, Clin Infect Dis 2010 Sawyer et al. New Engl J Med 2015 Montravers at al. Intensive Care Med (2018) 44:300–310 *(if source control)*
Cholecystitis & Cholangitis	4-5 days vs >7 days	De Santibañes et al. Surgery 2018 Regimbeau et al. JAMA. 2014 Jul;312(2):145-54 Doi et al. Clinical Microbiology and Infection 24 (2018) 1184e1189 *(if biliary drainage)* Srinu, The American Journal of Gastroenterology. 2024 Jan 1;119(1):176-182
Complex Appendicitis	1/2 days vs 5 days	Saar S, Mihnovits V,. J Trauma Acute Care Surg. 2019. 86:36-42. De Wijkerslooth E, Lancet 2023.
Post-Operative Prophylaxis	One-shot vs 1-5 days	De Jonge SW, Lancet Infect Dis. 2020; 20:1182-1192. ***General surgery*** Berry PS, Liver Transplant. 2019; 25(7):1043-1053 Nagata K, Yamada, K, Shinozaki T, et al. JAMA Network Open. 2022; ***Orthopedic***. Gahm J, JAMA Network Open. 2022;5(9):e2231583 ***Breast K*** Thurnheer MC, et al. JAMA Network Open.2024;7(10):e2439382. ***Cistectomy***

Meschiari's personal elaboration

SSTIs/osteomyelitis: antibiotic treatment duration

Type of infection	Duration	Evidence from RCTs and systematic meta-analysis
Cellulitis	**6 not inferior** to 12 days	Stevens et al., Clin Infect Dis 2014; 59:147 Moran GJ, Lancet Infect Dis 2014; 14(8): 696-705. Cranendonk DR. Clin Microbiol Infect. 2020 May;26(5):606-612.
SSTIs in Sacral Pressure Injuries & skin abscess	**5 days** (following abscess drainage if present)	Talan DA, N Engl J Med 2016; 374:823–32. Gottlieb M, Ann Emerg Med 2019; 73:8–16
NSTIs	**short (<7 days)** not inferior to long (>7) at least ***48 hours after source control***	Lyons NB. *Surg Infect (Larchmt)*. 2023;24(5): 425-432. Horn DL, Chan JD, Li K, et al. *Surg Infect* **2023**;24(8):741-748.
STIs without osteomyelitis in Diabetic foot infection	**10** non inferior to 21 days	Pham. Annals of Surgery 276(2):p 233-238, August 2022
Osteomyelitis in DFI, following debridement (but not curative amputation)	**3 weeks** vs 6 week following surgical debridement	Tone A, et a. Diabetes Care 2015;38:302-307 Gariani K, Clin Infect Dis. 2021 Oct 5;73(7):e1539-e1545.
Vertebral osteomyelitis	**6 weeks** versus 12 weeks ***Except for MRSA infection, undrained paravertebral/psoas abscesses, and ESRD***.	Bernard L. Lancet 2015. 385:875-82 Park KH, Clin Infect Dis. 2016 May 15;62(10):1262-1269.
Native joint bacterial arthritis	**2 weeks** vs 4 weeks After initial surgical lavage	Gjika E, Ann Rheum Dis. 2019 Aug;78(8):1114-1121.



Meschiari's personal elaboration

Recommended durations:

Shorter Is Better

Exceptions

Evidence from RCTs and observational studies

Antibiotic treatment duration: *Shorter Is Better* **Exceptions**

Type of infection	Duration	Evidence from RCTs
Prosthetic Joint infection Combined DAIR, 1-, and 2-Stage Exchanges	**6 week < 12 weeks**	Lora-Tamayo J, Int J Antimicrob Agents 2016;48:310-6. Bernard L, New Eng J Medicine 2021
Febrile cUTI in Men (prostatitis?)	**7 days < 14 days**	Laufarie M, Clin Infect Dis. 2023 (ofloxacin at a dose of 200 mg BID) PROSTASHORT
Urinary Tract Infections in Children	**5 days < 10 days**	Zaoutis T,. JAMA Pediatr. 2023;177(8):782-789. Montini G, Tessitore A, Pediatrics (2024) 153 (1): e2023062598.
Otitis Media	5 days < **10 days**	Hoberman A, New Eng J Medicine. 2016; 375:2446-2456. Kozyrskyj A, Cochrane Database Syst Rev 2010
Strep Throat infection	**3-5** days < **7-10 PNC**	Cochrane Database of Systematic Reviews 2021 Stahlgren GS, BMJ. 2019;367:l5337
Chronic Pulmonary Aspergillosis	**6 < 12-months**	Seghal IS, Lancet Infectious Diseases. 2022. 22(7):1052-1061.
***S.aureus* BSI without complications**	*2 vs > 2 weeks?*	***No data from RCT*** Fowler VG Jr, Arch Intern Med 2003 Chong YP, Antimicrob Agents Chemother 2013;57:1150e6. (relapse) Nicholas M. Brown, JAC Antimicrob Resist 2021 E.M. Eichenberger et al. Clinical Microbiology and Infection 26 (2020)
Complicated *S.aureus* BSI bacteremia	4 to **>6 weeks**	***No data from RCT*** Holland TL, JAMA 2018;320:1249e58. E.M. Eichenberger et al. Clinical Microbiology and Infection 26 (2020)
***P. aeruginosa* VAP?**	8 days < **14 days**	Bouglé A et al. Intensive Care Med (2022) 48:841–849 (Recurrence at day 90)

Meschiari's personal elaboration

Exceptions for BSI

- *S.aureus*
- *Non-fermenting gram negative bacilli*
- *Enterococci*
- *Candida* spp.

S.aureus

Clinical Microbiology and Infection 30 (2024) 1254–1260

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

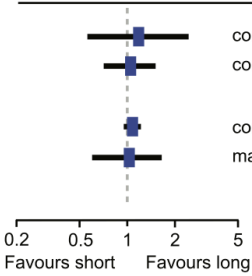
Systematic review

Long versus short course anti-microbial therapy of uncomplicated *Staphylococcus aureus* bacteraemia: a systematic review

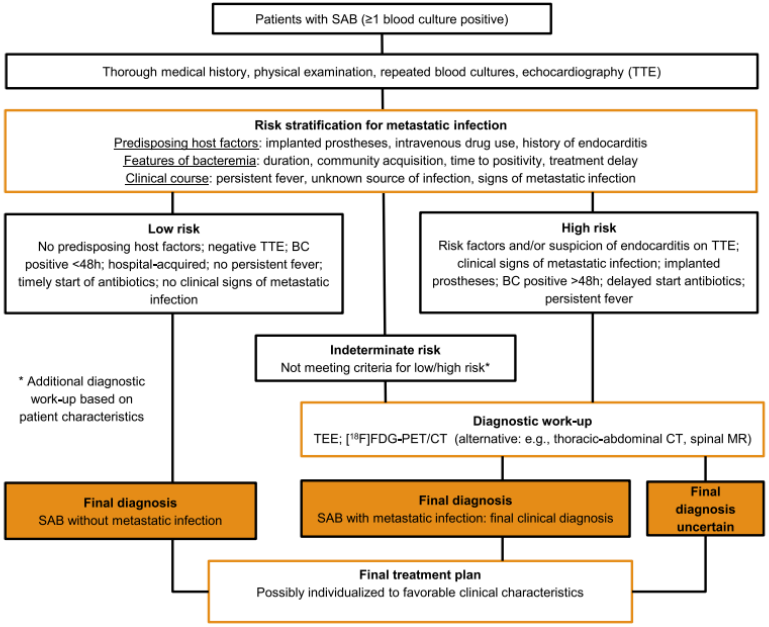
Martin Schnizer [1], Paul Schellong [1], Norman Rose [1], Carolin Fleischmann-Struzek [1], Stefan Hagel [1], Mohamed Abbas [2,3], Brendan Payne [4,5], Rebecca N. Evans [6], Mathias W. Pletz [1], Sebastian Weis [1,7,*]

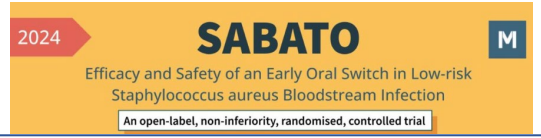
SAB without a known source should be treated for ≥14 days

Study	Outcome	DOT [Days]	# of patients	Estimate [95%−CI]
Abbas, 2020	90−day mortality	≤14 vs. >14	225	cond.adj. HR 1.18 [0.56
Thorlacius−U., 2021	90−day mortality	6-10 vs. 11-16	1005	cond.adj. OR 1.05 [0.71
Evans, 2021	28−day mortality	10-18 vs. >18	425	cond.adj. OR 1.08 [0.95−1.22]
Thorlacius−U., 2021	30−day mortality	6-10 vs. 11-16	1005	marg.adj. OR 1.03 [0.6−1.65]



Redefining S.aureus bacteremia: *a structured approach*





Kaasch AJ, Lancet Infect Dis. 2024 May;24(5):523-534.

Conclusions: Sound evidence that supports any duration of antibiotic treatment for patients with uncomplicated SAB is lacking.

ıKouijzer, V.G. Fowler Jr. and J. ten Oever Journal of Infection 86 (2023) 9–13
Schnizer M,. Clin Microbiol Infect. 2024 Oct;30(10):1254-1260.

Waiting for…Sab7/SAFE-trial/SNAP

S.aureus

Preferred antibiotic treatment duration based on primary source

J Antimicrob Chemother 2022; **77**: 2827–2834
https://doi.org/10.1093/jac/dkac237 Advance Access publication 23 July 2022

Journal of Antimicrobial Chemotherapy

Current clinical practice in antibiotic treatment of *Staphylococcus aureus* bacteraemia: results from a survey in five European countries

D. T. P. Buis[1]*, J. M. Prins[1], L. Betica-Radic[2], M. G. J. de Boer[3], M. Ekkelenkamp[4], D. Kofteridis[5], N. Peiffer-Smadja[6], J. Schouten[7], N. Spernovasilis[5,8], P. Tattevin[9], J. ten Oever[10] and K. C. E. Sigaloff[1] on behalf of the ESCMID Study Group for Antimicrobial Stewardship (ESGAP)

Antibiotic treatment duration (weeks)	Arthritis *n* (%)	Native valve endocarditis *n* (%)	Osteomyelitis *n* (%)	Pneumonia without abscess *n* (%)	Septic thrombophlebitis *n* (%)	Vertebral osteomyelitis without abscess *n* (%)
2	91 (17)	6 (1)	7 (1)	448 (84)	188 (35)	8 (1)
4	259 (48)	198 (37)	64 (12)	63 (12)	236 (44)	52 (10)
6	182 (34)	317 (59)	407 (76)	24 (4)	105 (20)	423 (79)
>6	4 (1)	15 (3)	58 (11)	1 (0)	7 (1)	53 (10)

Buis DTP et al. J Antimicrob Chemother. 2022 Sep 30;77(10):2827-2834.

Exceptions for enterococcal BSI

Clinical Microbiology and Infection 27 (2021) 364–371

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journal homepage: www.clinicalmicrobiologyandinfection.com

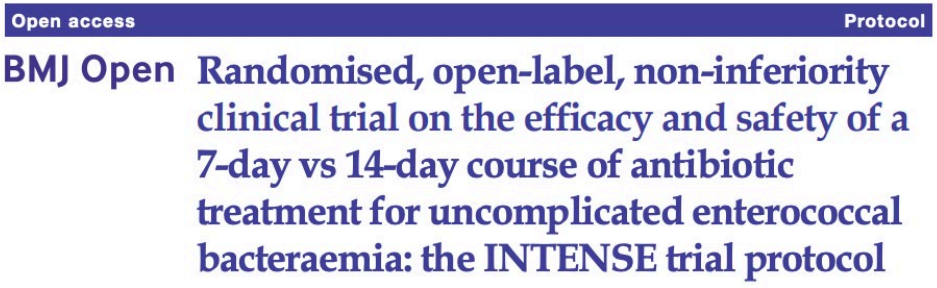
Narrative review

How do I manage a patient with enterococcal bacteraemia?

Elena Rosselli Del Turco [1,†], Michele Bartoletti [1,†], Anders Dahl [2], Carlos Cervera [3], Juan M. Pericàs [4,5,*]

[1] Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
[2] Department of Cardiology Herlev-Gentofte University Hospital, Copenhagen, Denmark
[3] Division of Infectious Diseases, University of Alberta, Edmonton, Canada
[4] Infectious Diseases Department, Hospital Clínic de Barcelona, Barcelona, Spain
[5] Vall d'Hebron Institute for Research (VHIR), Barcelona, Spain

- The length of therapy of non-complicated EB ranges from **7 to 14 days**.
- For **complicated EB** other than IE, the usual length of therapy is **4 weeks.**
- However, some cases may need longer courses For *E. faecalis IE*, the preferred options are ampicillin plus ceftriaxone (**6 weeks**) or ampicillin plus gentamicin (4 weeks in native valve IE and 6 weeks in prosthetic valve IE; a short regimen of 2 weeks of gentamicin might be used).



Open access Protocol

BMJ Open

Randomised, open-label, non-inferiority clinical trial on the efficacy and safety of a 7-day vs 14-day course of antibiotic treatment for uncomplicated enterococcal bacteraemia: the INTENSE trial protocol

Maldonado N, the INTENSE trial protocol. BMJ Open. 2023 Sep 6;13(9):e075699.

Exceptions for candidemia?

Questioning the 14-day dogma

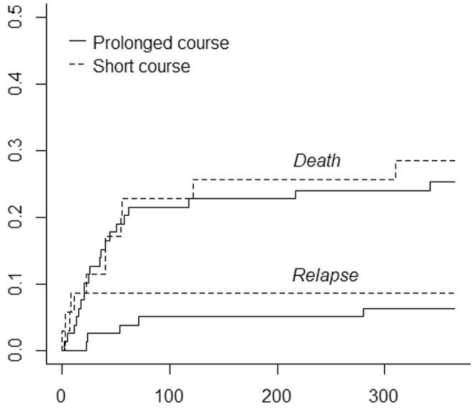
Potential advantage:

- Minimising patients' exposure to antifungal drugs reducing drug-resistant strains emerging.
- This approach becomes particularly pertinent in light of the increasing prevalence of *Candida glabrata*, *Candida parapsilosis* and multiresistant *Candida auris*

Table 3. Clinical Outcomes (90-Day and 1-Year All-Cause Mortality and Relapse) of Prolonged-Course Antifungal Therapy vs Short-Course Antifungal Therapy

	Univariable Analysis		Multivariable Analysis		IPTW-Adjusted HR	
Primary End Point	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause 90-d mortality	1.00 (0.43–2.30)	.99	0.47 (0.14–1.55)[a]	.22	0.67 (0.31–1.47)	.32
Secondary end points						
1-y recurrent *Candida* BSI	0.70 (0.17–2.93)[b]	.63	1.33 (0.30–6.00)[b,c]	.71	1.07 (0.20–5.80)[b]	.94
All-cause 1-y mortality	0.97 (0.46–20.60)	.95	0.58 (0.20–1.67)[d]	.32	0.72 (0.35–1.50)	.38

SC (5–11 days) or PC (12–24 days)



Limitations to treatment shortening strategies:

- deep organ candidiasis, chronic disseminated candidiasis or metastatic infection sites.
- Neutropenic patients: neutrophil function is crucial in eliminating Candida spp.
- suppurative thrombophlebitis, pacemakers, intraventricular devices and endovascular prostheses.
- Uncertain duration of ongoing candidemia or candidemia origin

In this decision-making process, the indispensable role of **infectious disease physicians**, is evident.

Vena A, Open Forum Infect Dis. 2022 Dec 8;10(1):ofac656.
Garcia et al. Mycoses. 2023;00:1–6.

Duration of antibiotic treatment for Gram-negative bacteremia – Systematic review and individual participant data (IPD) meta-analysis

Variable	Yahav et al.		von Dach et al.		Molina et al.		Mantel-Haenszel OR (95% CI)	Breslow–Day P value
	7 days (n = 306)	14 days (n = 298)	7 days (n = 169)	14 days (n = 165)	7 days (n = 117)	14 days (n = 127)		
90-d mortality	36 (11.8)	32 (10.7)	14 (8.3)	9 (5.5)	10 (8.5)	15 (11.8)	1.08 (0.73–1.58)	0.41
30-d mortality	16 (5.2)	12 (4.0)	6 (3.6)	4 (2.4)	4 (3.4)	8 (6.3)	1.08 (0.62–1.91)	0.40
Relapse of bacteremia –30d	8 (2.6)	8 (2.7)	2 (1.2)	3 (1.8)	7 (5.9)	6 (4.7)	1.00 (0.50–1.97)	0.82
Readmissions - 30d	74 (24.2)	79 (26.5)	14 (8.3)	9 (5.5)	11 (9.2)	12 (9.3)	0.98 (0.73–1.33)	0.49
Hospital length of stay, Median (IQR)	1 (0–4)	1 (0–4)	4 (1.3–10)	4 (1–11)	4 (0–9)	3 (0–8)	–	0.71*
Duration of antibiotic therapy, Median (IQR)	5 (4–13)	12 (10–16)	7 (6–9)	13 (9–14)	7 (7–14)	14 (14–16)	–	0.39*
Local suppurative complications 90d	16 (5.2)	10 (3.4)	2 (1.2)	1 (0.6)	–	–	1.62 (0.76–3.47)	0.87
Distal complications 90d	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	–	–	2.00 (0.18–22.08)	–
Emergence of resistance to study antibiotic –90d	33 (10.8)	29 (9.7)	3 (1.8)	0 (0.0)	–	–	1.23 (0.74–2.04)	0.11
Diarrhea	18 (5.9)	24 (8.1)		–	2 (1.7)	3 (2.3)	0.73 (0.40–1.33)	1.00
Clostridioides difficile infection	2 (0.7)	2 (0.7)	2 (1.2)	4 (2.4)	–	–	0.65 (0.18–2.31)	0.60
Rash	2 (0.7)	4 (1.3)	–	–	1 (0.8)	4 (3.1)	0.37 (0.10–1.41)	0.67
Acute kidney injury	14 (4.6)	12 (4.0)	–	–	3 (2.5)	1 (0.8)	1.33 (0.64–2.77)	0.37

Data are presented as no. (%). OR – odds ration; CI – confidence interval; IQR - interquartile range. *P value by General linear models.

Table 2: **The association between study arm and outcomes, stratified by trial (For categorical variables, fixed-effect meta-analysis model, Mantel-Haenszel method. Homogeneity of odds ratios between trials was evaluated with the Breslow–Day test).**

30-d mortality	All patients		16/306 (5.2)	12/298 (4.0)	6/169 (3.6)	4/165 (2.4)	4/117 (3.4)	8/127 (6.3)	1.08 (0.62–1.91)	0.40
	Gender	Women	7/156	7/163 (4.3)	4/107 (3.7)	2/94 (2.1)	3/59 (5.1)	2/59 (3.4)	1.26 (0.56–2.82)	0.49
		Men	9/150 (6.0)	5/135 (3.7)	2/62 (3.2)	2/71 (2.8)	1/58 (1.7)	6/68 (8.8)	0.93 (0.42–2.09)	
	Source of infection	Non UTI	7/86 (8.1)	5/107 (4.7)	2/68 (2.9)	2/53 (3.8)	3/48 (6.3)	3/63 (4.8)	1.35 (0.57–3.18)	0.40
		UTI	9/220 (4.1)	7/191 (3.7)	4/101 (4.0)	2/112 (1.9)	1/69 (1.4)	5/64 (7.8)	0.94 (0.44–2.00)	
	SBP	SBP≥100	13/215 (6.0)	11/202 (5.4)	3/106 (2.8)	2/117 (1.7)	2/88 (2.3)	3/93 (3.2)	1.14 (0.57–2.27)	0.76
		SBP<100	3/91 (3.3)	1/95 (1.1)	3/63 (4.8)	2/47 (4.3)	2/29 (6.9)	5/34 (14.7)	0.96 (0.35–2.62)	
	Age	Age<65	7/98 (7.1)	2/102 (2.0)	0/28 (0.0)	0/39 (0.0)	2/57 (3.5)	2/57 (3.5)	2.51 (0.76–8.29)	0.29
		Age≥65	9/208 (4.3)	10/196 (5.1)	6/141 (4.3)	4/126 (3.2)	2/60 (3.3)	6/70 (8.6)	0.81 (0.42–1.56)	
	Immunosuppression	No	11/237 (4.6)	12/217 (5.5)	/	/	3/100 (3.0)	7/113 (6.2)	0.71 (0.35–1.44)	0.06
		Yes	5/69 (7.2)	0/81 (0.0)	/	/	1/17 (5.9)	1/14 (7.1)	7.05 (0.83–59.80)	

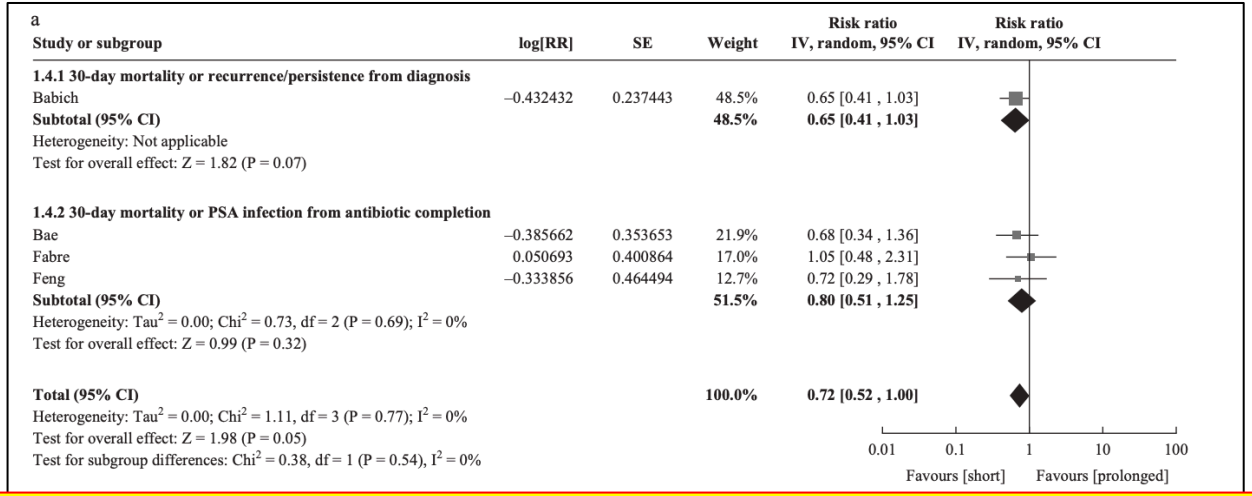
	Yahav et al. (2018)	von Dach et al. (2020)	Molina et al. (2021)
(Continued from previous page)			
Bacteria type			
Escherichia coli	380/604 (63%)	377/502 (74%)	155/247 (63%)
Klebsiella spp	80/604 (13%)	68/502 (14%)	46/247 (19%)
Other	82/604 (14%)	45/502 (9%)	46/247 (19%)
Enterobacteriaceae			
Non-fermenting bacilli	61/604 (10%)	None	None
Other[b]	1/604 (~0%)	12/502 (2%)	None
Recurrent bacteremia (previous 60 days)	NR	None	NR
Multidrug resistant (MDR) bacteria[c]	109/604 (18%)	40/504 (8%)	41/248 (16.5%)
Infection characteristics			
Source of infection			
Urinary tract	411/604 (68%)	335/504 (66%)	136/248 (55%)
Abdominal	71/604 (12%)	80/504 (16%)	34/248 (14%)
Respiratory	24/604 (4%)	25/504 (5%)	15/248 (6%)
Central venous catheter	38/604 (6%)	8/504 (2%)	30/248 (12%)
Skin and soft tissue	9/604 (2%)	4/504 (1%)	3/248 (1%)
Unknown	51/604 (8%)	52/504 (10%)	29/248 (12%)
Presence of hypotension on initial presentation (SBP<100)	186/604 (31%)	169/504 (34%)	63/244 (26%)
Hospital acquired	176/604 (29%)	135/504 (27%)	81/247 (33%)

For patients hemodynamically stable and afebrile at 48 h prior to discontinuation, ***7 days of antibiotic therapy for enterobacterales bacteremia*** result in similar outcomes as 14 days, in terms of mortality, relapse, LOS, complications of infection, resistance emergence, and AEs.

Adi Turjeman; eClinicalMedicine 2023;55: 101750

Short versus prolonged duration of therapy for Pseudomonas aeruginosa BSI: *a systematic review and meta-analysis*

Variables	Babich et al., 2022 [23]		Bae et al., 2021 [24]		Fabre et al., 2019 [27]		Feng et al., 2023 [28]	
	Short (*N* = 274)	Prolonged (*N* = 384)	Short (*N* = 97)	Prolonged (*N* = 193)	Short (*N* = 69)	Prolonged (*N* = 180)	Short (*N* = 229)	Prolonged (*N* = 205)
Age (years)	68 (58–79)	67 (54–76)	64 (53–73)	64 (55–72)	61 (48–76)	66 (52–76)	39 (24–51)	42 (27–52)
Male	171 (62.6)	251 (65.4)	64 (66.0)	123 (63.7)	43 (62.3)	112 (62.2)	128 (55.9)	109 (53.2)
Pitt bacteraemia score	NR	NR	2 (0–3)	2 (0–3)	2 (2–3)	2 (1–3)	NR	NR
ICU admission	40 (14.7)	65 (17)	6 (6.2)	23 (11.9)	21 (30.4)	54 (30.0)	NR	NR



Conclusions: short duration of antimicrobial therapy may have similar efficacy to prolonged treatment for PSA-BSI.
Future **randomized trials** will be necessary to definitively determine optimal management of PSA bacteraemia.

SITA Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina

N. Ranganath et al. / Journal of Hospital Infection 148 (2024) 155e166

Waiting for… SHORTEN-2, OPTIMISE and BALANCE RCTs..

Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections

Author: The BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network* Author Info & Affiliations

Published November 20, 2024 | DOI: 10.1056/NEJMoa2404991 | Copyright © 2024

74 hospitals in seven countries, 3608 patients

Excluding criteria: severe immunosuppression, foci requiring prolonged treatment, single cultures with possible contaminants, or ***Staphylococcus aureus.***

- 55.0% of patients were in the ICU and 45.0% were on hospital wards.
- Infections were acquired in the community (75.4%), hospital wards (13.4%) and ICUs (11.2%).
- Bacteremia most commonly originated from the UT (42.2%), abdomen (18.8%), lung (13.0%), vascular catheters (6.3%), and SSTIs (5.2%).
- By 90 days, 261 patients (14.5%) receiving antibiotics for 7 days had died and 286 patients (16.1%) receiving antibiotics for 14 days died (difference, −1.6 percentage points [95.7% confidence interval {CI}, −4.0 to 0.8])

- These findings were generally consistent across secondary clinical outcomes and across prespecified subgroups defined according to patient, pathogen, and syndrome characteristics.

N. Ranganath et al. / Journal of Hospital Infection 148 (2024) 155e166

Exceptions for VAP ?

ORIGINAL

Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial

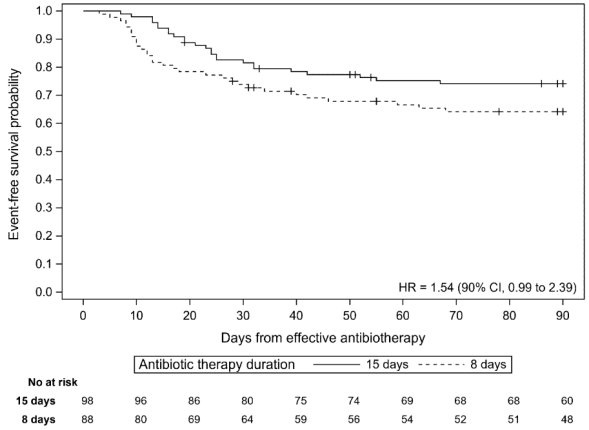
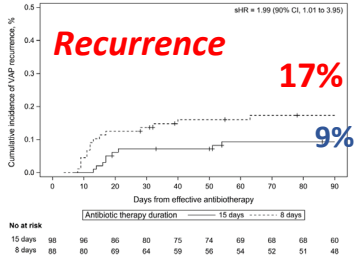


Fig. 2 Event-free survival curves of the survival probability for VAP recurrence or death in ICU (Kaplan–Meier estimates) in the ITT population. Survival probability is for the 90 days since the start of effective antibiotic therapy as a function of the duration of antibiotic therapy

Table 3 Secondary outcomes, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (95% CI)
Duration of mechanical ventilation, days[a]	25 (15.5–35)	22 (12–41)	−3 (−9 to 5)
Duration of ICU stay, days	34 (23–56)	34 (20–54)	0 (−7 to 6)
Exposure to antibiotics during ICU stay, days	23 (15–34)	18 (11.5–28.5)	−5 (−9 to 0)
Number of extra pulmonary infections during ICU stay[a]	1 (0–2)	1 (0–2)	0 (−1 to 1)
Acquisition of MDR pathogens during ICU stay—no. (%)	24/97 (24.7)	17/84 (20.2)	−4.5% (−16.8 to 8.3%)



The percentage of recurrence of PA-VAP during the ICU stay was 9.2% in the 15-day group versus 17% in the 8-day group.

BUT

Unbalanced time at risk for recurrence!

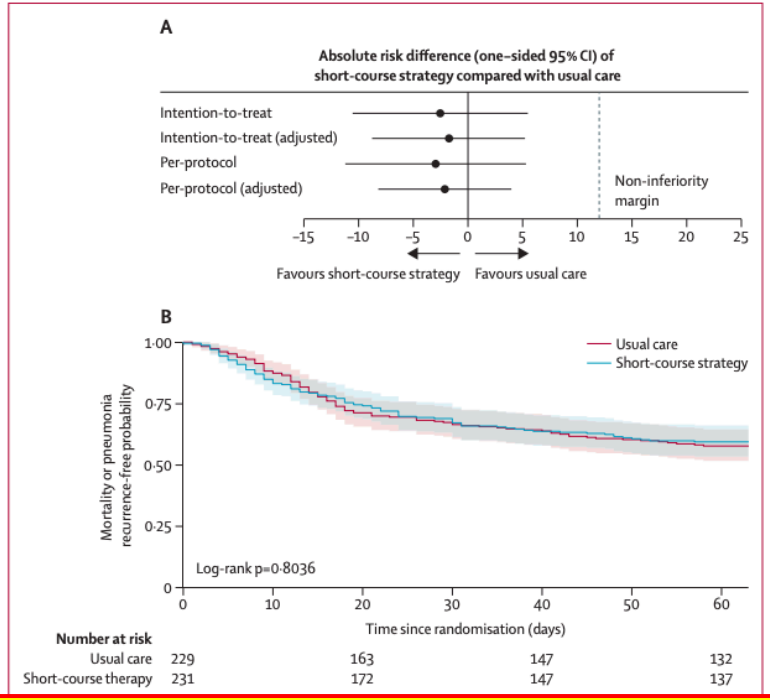
Take-home message

The optimal duration of treatment for *Pseudomonas aeruginosa* ventilator-associated pneumonia remains unknown. In a prospective randomized trial, we did not demonstrate the non-inferiority of a short duration (8 days) of antibiotic therapy.

Bouglé A, Intensive Care Med. 2022 Jul;48(7):841-849. doi: 10.1007/s00134-022-06690-5.

Individualised, short-course antibiotic treatment versus usual long-course treatment for VAP (REGARD-VAP): a *multicentre, individually randomised, open-label, non-inferiority trial*

Participants were randomized until **fever resolution for 48 h and haemodynamic** stability, to individualised **short-course treatment (≤7 days) or usual care (≥8 days**, with precise durations determined by the primary clinicians).



	Short-course group (n=211)	Usual care group (n=224)	Unadjusted estimates (95% CI; p value)	Adjusted estimates (95% CI; p value)*
Mean (SD) duration of antibiotics during admission, days	20·5 (15·0)	25·7 (15·1)	−5·2 (−8·1 to −2·4; 0·0003)	−5·2 (−7·5 to −2·8; 0·0003)
Mean (SD) duration of mechanical ventilation during admission, days†	29·8 (27·6)	30·0 (27·1)	−0·06 (−5·2 to 5·1; 0·98)	0·14 (−4·2 to 4·5; 0·95)
Mean (SD) duration of ICU admission, days	27·0 (24·2)	28·5 (24·2)	−1·4 (−6·0 to 3·1; 0·54)	−1·3 (−5·2 to 2·5; 0·57)
Mean (SD) duration of stay in hospital, days	35·1 (23·8)	35·0 (23·0)	0·22 (−4·2 to 4·6; 0·92)	−0·15 (−3·8 to 3·5; 0·95)
Readmission to an acute care hospital	40 (19%)	40 (18%)	0·011% (−0·066 to 0·088%; 0·86)	0·014% (−0·047 to 0·074%; 0·71)
Pneumonia recurrence determined by at least one independent assessor	37 (18%)	39 (17%)	0·0013% (−0·071 to 0·074%; 1·00)	0·0010% (−0·057 to 0·059%; 0·98)
Bloodstream infection after enrolment	26 (12%)	30 (13%)	−0·011% (−0·078 to 0·056%; 0·85)	−0·013% (−0·066 to 0·040%; 0·69)
Newly colonised or infected with carbapenem-resistant Gram-negative bacilli after enrolment	37 (18%)	41 (18%)	−0·0077% (−0·084 to 0·069%; 0·93)	−0·0009% (−0·061 to 0·059%; 0·98)
Acute kidney injury‡	11 (5%)	79 (35%)	−30% (−38 to −23%; <0·0001)	−30% (−36 to −24%; <0·0001)
Drug-induced liver injury§	1 (<1%)	2 (1%)	−3% (−6 to 0; 0·093)	−3% (−5 to −1%; 0·033)
Diarrhoea	4 (2%)	5 (2%)	0 (−3 to 3%; 1·00)	−1% (−3 to 2%; 0·69)
Allergy (eg, DRESS, rash, SJS)	1 (<1%)	2 (1%)	0 (−2 to 2%; 1·00)	−1% (−2 to 1%; 0·36)
Any antibiotic side-effects	17 (8%)	86 (38%)	−30% (−38 to −23%; <0·0001)	−31% (−37 to −25%; <0·0001)

Key concepts:

- No immunocompromised
- No SOFA > 11
- Median age 64 years (IQR 51–74)
- 30% VAP episodes were culture-negative.
- Most were Gram-negative 94%;
- 258 (53%) were **Gram-negative non-fermenting bacilli.**
- **34% CRE; 18% ESBL**

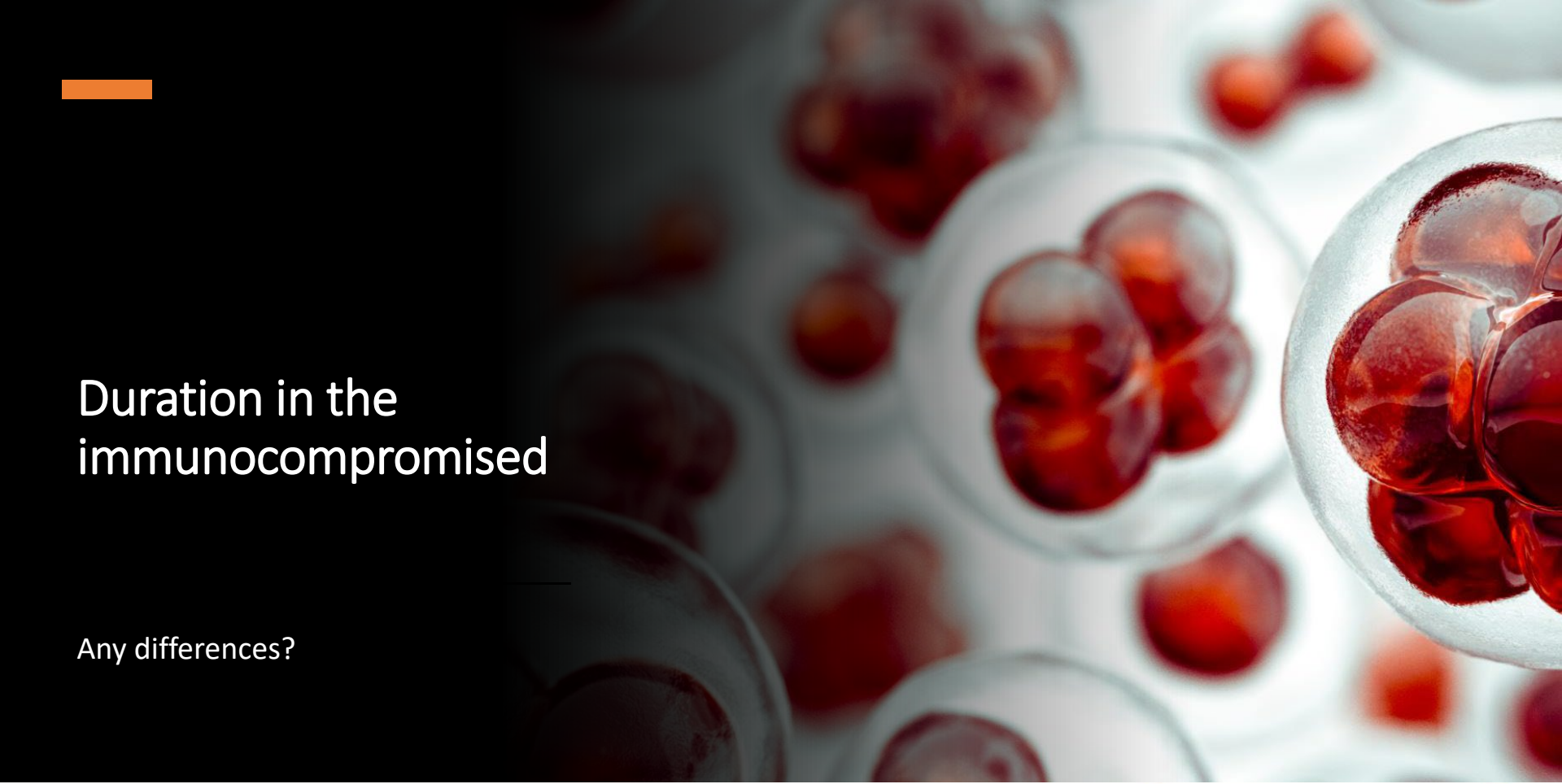
No differences among groups

Key concept: individualised shortened antibiotic duration!!

Mo Y, Lancet Respir Med. 2024 May;12(5):399-408.

Duration in the immunocompromised

Any differences?



How long therapy for FN

Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

Manuela Aguilar-Guisado, Ildefonso Espigado, Almudena Martín-Peña, Carlota Gudiol, Cristina Royo-Cebrecos, José Falantes, Lourdes Vázquez-López, María Isabel Montero, Clara Rosso-Fernández, María de la Luz Martino, Rocío Parody, José González-Campos, Sebastián Garzón-López, Cristina Calderón-Cabrera, Pere Barba, Nancy Rodríguez, Montserrat Rovira, Enrique Montero-Mateos, Jordi Carratalá, José Antonio Pérez-Simón, José Miguel Cisneros

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	..	..
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	−2·4 (−4·6 to −0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (−1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	..	..
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	−3·8 (−6·1 to −1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (−1·1 to 2·8)	0·38
Modified per-protocol population				
Number of patients (%)	36 (46%)	30 (38%)	..	..
Efficacy variable				
EAT-free days	17·5 (6·4)	11·3 (7·0)	−6·4 (−9·7 to −3·0)	0·0003
Safety variables				
Crude mortality	0 (0)	0 (0)	NA	1·00
Days of fever	4·9 (5·4)	5·4 (6·3)	0·5 (−2·4 to 3·4)	0·72

Data are n (%) or mean (SD), unless otherwise stated. EAT=empirical antimicrobial therapy. NA=not applicable.

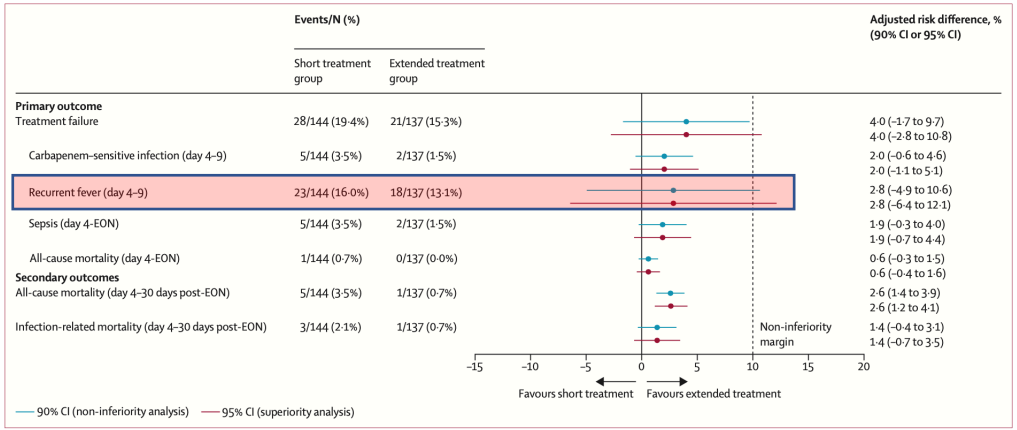
Table 3: Efficacy and safety endpoints

EAT was withdrawn after 72 h or more of apyrexia plus clinical recovery;
(Control group, treatment was withdrawn when the neutrophil count was also 0·5 × 109L)

Short versus extended treatment with a carbapenem in patients with high-risk fever of unknown origin during neutropenia: a non-inferiority, open-label, multicentre, randomised trial

*fixed short treatment **(3 days)** compared with an extended treatment **(9–14 days)***

Nick A de Jonge, Jonne J Sikkens*, Sonja Zweegman, Aart Beeker, Paula Ypma, Alexandra H Herbers, Wies Vasmel, Arne de Kreuk, Juleon L L M Coenen, Birgit Lissenberg-Witte, Mark H H Kramer, Michiel A van Agtmael*, Jeroen J W M Janssen**

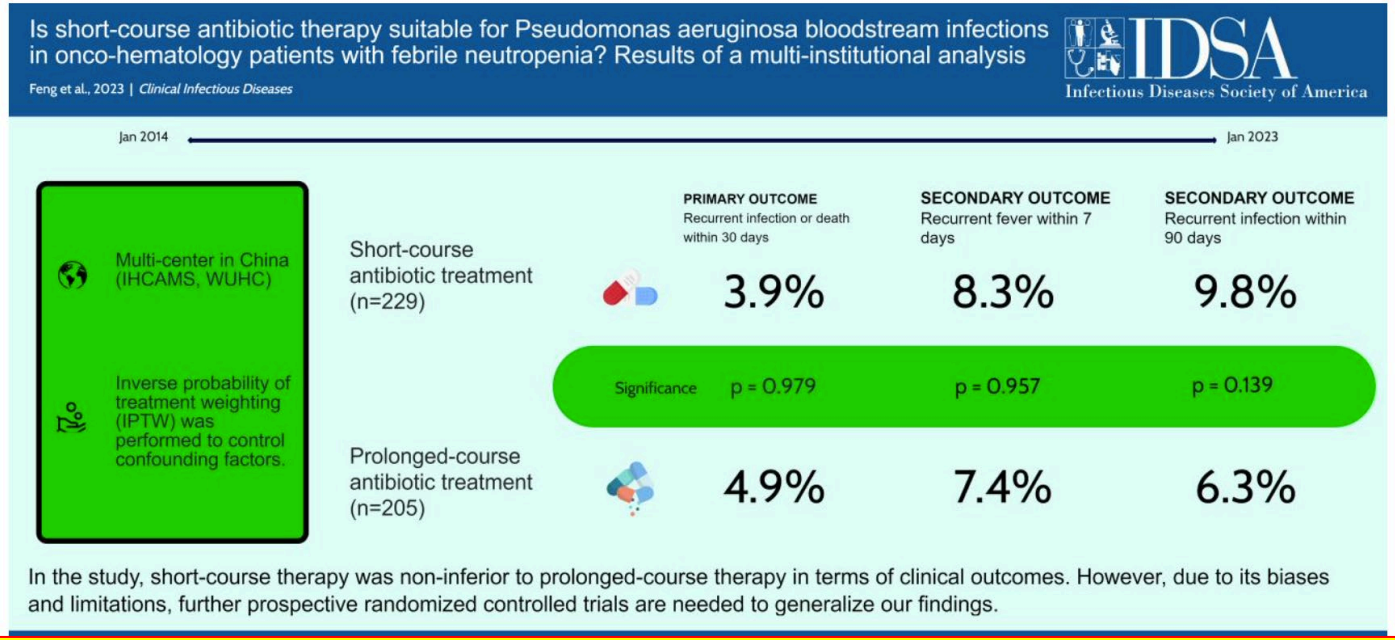


None of the deaths were related to carbapenem-sensitive infections.
Early discontinuation of carbapenem treatment in patients with febrile neutropenia of unknown origin **does not result in increased treatment failure.**
Our study supports short treatment if patients are afebrile after 3 days of carbapenem treatment.

Aguilar-Guisado M. Lancet Haematol. 2017;4(12):e573–83.
Lancet Haematol 2022; 9: e563–72

Is Short-course Antibiotic Therapy Suitable for *Pseudomonas aeruginosa* BSIs in Onco-hematology Patients With Febrile Neutropenia?

Results of a Multi-institutional Analysis



Limitations: Low prevalence of comorbidities due to our populations being predominantly **young** & 50% of cases were **primary BSI.**

- ***Primary factors recurrence and mortality were***: ***MDR bacterial infections, perianal or pulmonary infections***, and persistent or recurrent hematological malignancies, **neutropenia non-recovery**.

Feng X, Clin Infect Dis. 2024 Mar 20;78(3):518-525.

How to implement descalation strategies?

Evidences and Real-life strategies

Modena Antibiotic Stewardship Programme
at hospital level

AIM: Assess whether an Electronic Clinical Decision Support Systems (eCDSS) combined with infectious disease (ID) clinicians progressive feedback can improve antimicrobial stewardship (AMS) indicators for adults admitted to tertiary care hospitals.

ASP GUIDELINES 2007

CORE ELEMENTS
- Formulary restriction with re-authorisation of named anti-infectives
- Prospective audit with intervention and feedback
- Multidisciplinary AMS team
- Guideline development

ADDITIONAL ELEMENTS
- De-escalation of therapy based on culture results
- Dose optimisation
- IV to PO switch
- Education
- Antimicrobial order forms
- Antimicrobial cycling
- Combination antimicrobial therapy
- Information technology to provide decision support and enhanced surveillance
- Antibiograms - at patient and organisation level

Barlam TF, Clin Infect Dis. 15 maggio 2016;62(10):e51–77

MODENA ANTIMICROBIAL STEWARDSHIP

CORE ELEMENTS
- ✓ ✓Advisory services: request on electronic agenda-urgent calls
- ✓ ✓Control of high-cost drug prescriptions within 48 hours of prescription
- ✓ ✓Clinical audits with direct feedback on the 'Adopt-a-Department' field
- ✓ ✓Identification of an AS team
- ✓ ✓Development of empirical therapy guidelines and treatment algorithms for hospital infections

ADDITIONAL ELEMENTS

✓**Computer tool (Database) shared between pharmacists and infectivologists for monitoring antibiotics-antifungals with high ecological and economic impact** (patient identification and delivery of therapies max. for 72 h)

✓Report on consumption of all antibiotics-antifungals by home made management control software (Fac VIEWER) Report on prescriptive appropriateness per therapeutic indication and monitoring adherence to guidelines

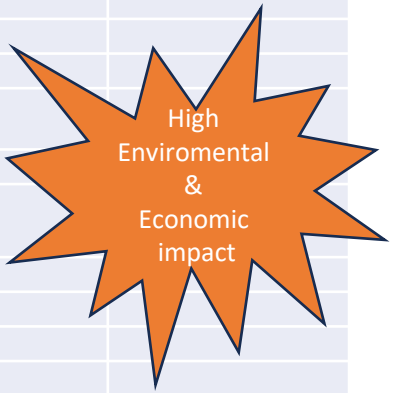
✓*Experimental ecological* models*for identifying prescriptive thresholds for the hospital*

Meschiari's personal data

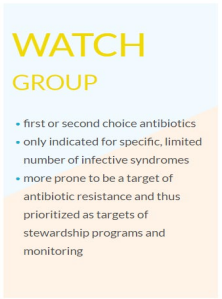
Materials and Methods

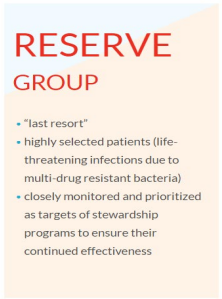
- Prospective observational study conducted **from April 2022 to April 2024** in the 1200-bed tertiary care referral University Hospital of Modena, northern Italy.
- Since April 2022 an **Electronic Clinical Decision Support Systems** (eCDSS), integrating patient-specific data of antimicrobial prescriptions with pharmacy information by an automatic alert, was implemented.

Antibiotics		Antifungals	Others
Ampicillin-sulbactam	Fidaxomicin	Anidulafungin	Bezlotoxumab
Aztreonam	Fosfomycin	Caspofungin	
Cefiderocol	Imipenem	Micafungin	
ceftaroline	Imipenem-relebactam	Isavuconazole	
Ceftazidime-avibactam	Linezolid	Voriconazole	
Ceftobiprole	Meropenem		
Ceftolozane-tazobactam	Meropenem-vaborbactam		
Dalbavancin	Oritavancin		
Daptomycin	Tedizolid		
Ertapenem	Tigecyclin		
Eravacycline			



All these antimicrobial prescriptions must be required through an **informatic motivated request form** at the hospital pharmacy and automatically reported in a shared database between pharmacists and infectious disease specialists involved in AMS implementation





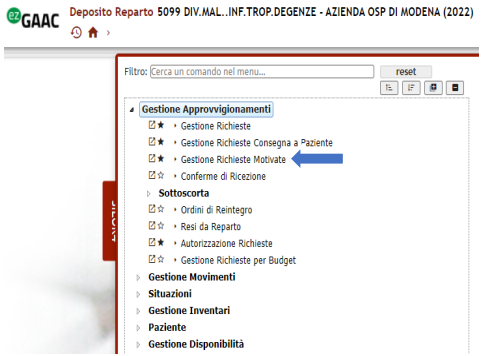
World Health Organization (WHO). AWaRe classification of antibiotics for evaluation and monitoring of use, 2023 https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04

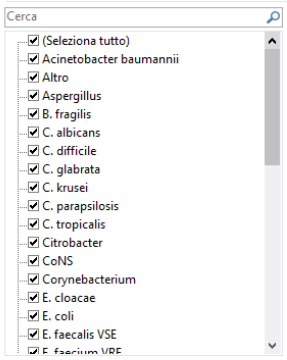
DATABASE

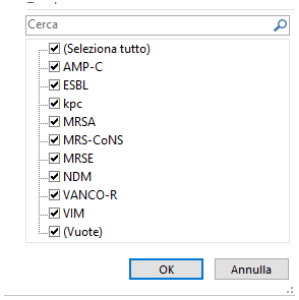
- Prescriptive appropriateness
- Surveillance and research
- -Health and economic optimisation

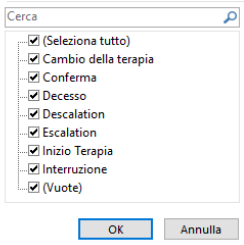
PHARMACIST

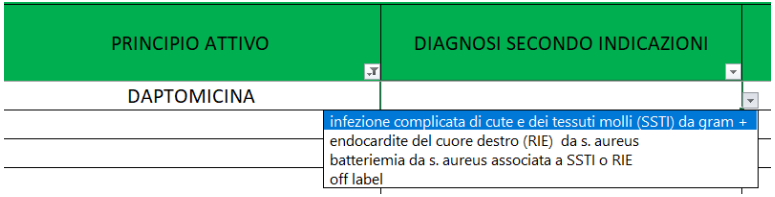
- Department requesting the drug
- Basic demographic data
- Type of antibiotic prescribed and its dose









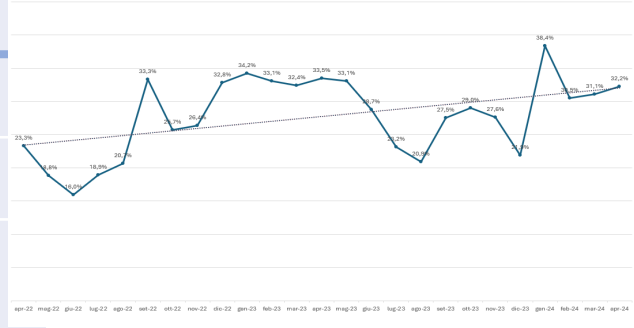


CLINICIAN

- Start/end date of the prescription
- ID counseling (telephone/in person)
- Indications for each molecule according to AIFA
- Presence of bacteremia
- Empirical/targeted therapy
- Accordance with hospital guidelines for empirical therapies
- Identified pathogens and mechanisms of resistance for targeted therapies
- Types and timing of AS interventions

	Total (5925)	April 2022 April 2023	May 2023 – April 2024	P value
Days of therapy according to indication, mean (±SD)				
UTIs	6.9 (5.8)	7.0 (6.1)	6.7 (5.5)	0.456
RTIs	6.8 (3.9)	7.1 (4.4)	6.4 (3.3)	**<0.001**
IAIs	8.9 (6.4)	9.4 (6.7)	8.3 (5.9)	**0.012**
SSTIs	9.3 (8.6)	9.9 (9.6)	8.6 (7.5)	**0.026**
Prescriptions with at least two evaluations, N (%)	2917(49.2%)	1172 (42.6%)	1745 (55.0%)	**0.001**
Number of evaluations for each prescription, mean (±SD)	1.57 (0.21)	1.49 (0.71)	1.66 (0.81)	**0.001**
ASP interventions, total	9336	4572	4764	
Type of intervention, N (% of the interventions)				
Start	2110/9336 (22.6%)	1014/4572 (22.2%)	1096/4764 (23.0%)	0.053
Confirm	3099/9336 (33.2%)	1432/4572 (31.3%)	1667/4764 (35.0%)	**0.001**
Switch	428/9336 (4.6%)	312/4572 (6.8%)	116/4764 (2.4%)	**<0.001**
Stop	2562/9336 (27.4%)	1196/4572 (26.2%)	1366/4764 (28.7%)	**0.050**
Escalation	172/9336 (1.8%)	69/4572 (1.5%)	103/4764 (2.2%)	0.071
Descalation	541/9336 (5.8%)	220/4572 (4.8%)	321/4764 (6.7%)	**0.001**
Others	424/9336 (4.5%)	229/4572 (5.0%)	195/4764 (4.1%)	0.056
Deprescribing on total intervention, N (%)	3103/9336 (33.2%)	1416/4572 (30.9%)	1687/4764 (35.4%)	**0.001**

Deprescribing ("stop" and "descalation") on total evaluations per month



Results

Changes in patterns of antimicrobial prescription within one years after the introduction of an eCDSS for AMS implementation

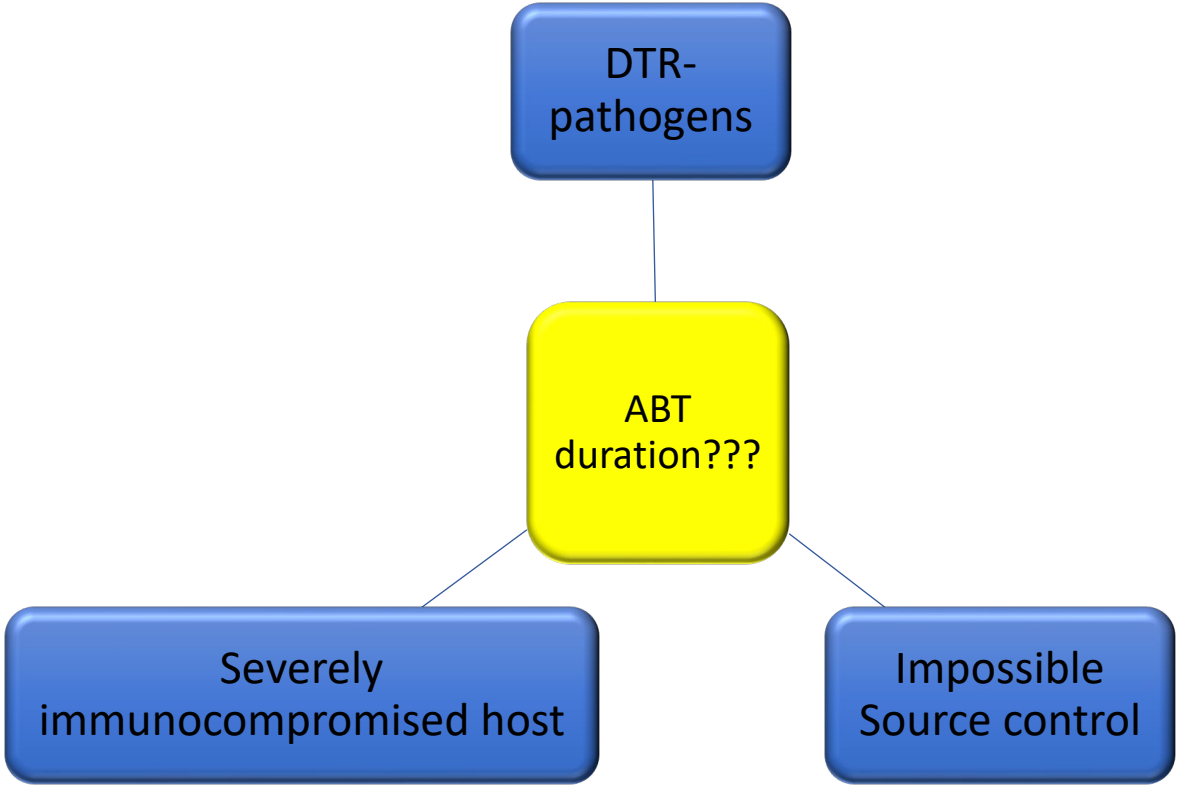
Univariate and multivariate analysis
factors associated with **deprescribing ("stop" & "descalation") interventions**

	Univariate			Multivariate		
Covariate	OR	95% CI	P value	aOR	95% CI	P value
ID prescription	1.35	1.20-1.52	**0.001**			
More than one evaluation	2.48	2.43-2.53	**<0.001**	2.41	2.16-2.69	**<0.001**
Off label indication	0.94	0.83-1.05	0.272			
Bacteremia	1.11	0.99-1.24	0.077			
Medical ward	0.96	0.87-1.06	0.420			
Surgical ward	0.91	0.80-1.05	0.183			
ICU ward	1.21	0.08-1.36	**0.001**	1.22	1.08-1.38	**0.001**
Second period of observation	1.23	1.12-1.43	**0.048**	1.26	1.12-1.31	**<0.001**
Carbapenems	1.19	1.07-1.32	**0.001**	1.48	1.30-1.69	**<0.001**
Oxazolidinones	1.17	1.04-1.32	**0.011**	1.64	1.41-1.90	**0.001**
Daptomycin	1.28	1.10-1.49	**0.001**	1.96	1.63-2.34	**0.001**
Tigecycline	0.90	0.75-1.09	0.273			
Bli/blic	1.14	0.89-1.46	0.311			
Antifungals	1.51	1.29-1.78	**0.001**			
UTI	1.19	1.00-1.41	**0.046**	1.19	0.99-1.42	0.067
CAP	0.92	0.71-1.20	0.554			
HAP	1.15	1.01-1.31	**0.035**			
IAI	1.03	0.89-1.18	0.700			
ABSSI	1.21	1.01-1.46	**0.041**			
Prosthetic matherial infection	0.39	0.21-0.72	**0.002**			
Gram positive microrganisms	0.83	0.72-0.96	**0.013**	0.75	0.64-0.88	**<0.001**
Gram negative microrganisms	0.92	0.82-1.03	0.158			

Final considerations

Future perspectives

The real challenge



Short course antibiotics for common infections: *Take-home messages*

- Designing clinical trials to assess **appropriate antibiotic durations** can be challenging
- Recent RCTs have commonly used a **non- inferiority** design to assess clinical outcomes, such as *clinical cure*.
- However, the endpoints for some studies may include ***outcomes*** not irrelevant to patients or clinicians, such a:

✓*microbiological cure*
✓*AMR*
✓*Others Aes (CDIs)*

- Lack of RCTs evaluated duration *per pathogens* more than for site of infection (not specified if BSI y/n)
- Too restrictive ***inclusion/exclusion criteria*** in RCTs (haemodynamic instability, Polymicrobial growth, IDs..)
- Complicated infections is a ***dynamic concept and could be reversed***
- ***In these complicated scenarios, you will to individualize treatment duration basing on clinical response and risk of recurrence***

what do we Know and where do we Go from Here?

Lee RA et al. Clin Microbiol Infect 2022 (29 August)
McDonald E et al. Clin Microbiol Infect 2022 Sept 1
&Meschiari's personal considerations

Open Forum Infectious Diseases

PERSPECTIVES

Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV

Kusha Davar,[1] Devin Clark,[1] Robert M. Centor,[2] Fernando Dominguez,[1] Bassam Ghanem,[3] Rachael Lee,[4] Todd C. Lee,[5] Emily G. McDonald,[6] Matthew C. Phillips,[7,8] Parham Sendi,[9] and Brad Spellberg[1]

Table 2. Summary of Randomized Controlled Trials of Oral vs IV-Only Therapy

Diagnosis	No. of RCTs Demonstrating IV > Oral	No. of RCTs Demonstrating Oral ≥ IV	References
Osteomyelitis	0	9 (all equal)	[103–111]
Bacteremia	0	10 (8 equal, 2 superior cure for oral)	[109, 112–120]
Endocarditis	0	3 (2 equal, 1 superior mortality for oral)	[121–123]

Abbreviations: IV, intravenous; RCT, randomized controlled trial.

(1) the patient is clinically and hemodynamically stable;
(2) procedural source control ideally with clearance of bacteremia;
(3) the patient's gut is functioning and likely to absorb oral medications;
(4) a published regimen is available for the target pathogen

With the shared goal of bettering patient care..
"Oral is the new IV" needs to be more than just a motto.
It is time to make that switch, both in our mind-set and in practice..

Davar K, et al. Open Forum Infect Dis. 2022 Dec 29;10(1)
Clinical Microbiology and Infection 29 (2023) 1117e1119

Clinical Infectious Diseases

MAJOR ARTICLE

Early Oral Antibiotic Switch in *Staphylococcus aureus* Bacteraemia: The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Trial Early Oral Switch Protocol

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thank you for your attention

& thanks to..